September 7, 2005

GlaxoSmithKline Inc.
7333 Mississauga Road North
Mississauga, Ontario
Canada L5N 6L4

Health Canada Endorsed Important Safety Information on PrSEREVENT®

Re: Important Updated Safety Information for SEREVENT® and Reminder of its Appropriate Use in Patients with Asthma

Dear Health Care Professional,

GlaxoSmithKline Inc. (GSK) in consultation with Health Canada, would like to inform you that the product monographs (PM) of SEREVENT®/SEREVENT® DISKHALER®/SEREVENT® DISKUS® and ADVAIR®/ADVAIR® DISKUS® have been updated to include the results of the United States Salmeterol Multi-Center Asthma Research Trial (SMART). The preliminary results were previously communicated in August 2003 via a "Dear Health Care Professional Letter". The revisions to the PMs are generally consistent with the outcome of the FDA's Pulmonary-Allergy Drugs Advisory Committee (PADAC) during their review of the safety of the long-acting beta$_2$-agonists (salmeterol and formoterol) on July 13, 2005.

Key Messages

- Long-acting beta$_2$-agonists, such as SEREVENT®, are an alternative additional therapy for patients with asthma who have unsatisfactory symptom control despite an optimal dose of inhaled corticosteroids (ICS). In asthma, they must be used in conjunction with an optimal dose of inhaled corticosteroids (ICS) and should never be used as rescue medication.
- In cases of asthma exacerbation, increasing the daily dosage of SEREVENT® is not appropriate.
- In SMART, there was an increased risk of asthma-related death and other serious respiratory-related outcomes in patients who used SEREVENT® vs. placebo, in addition to their usual asthma therapy[1].
- Post hoc analysis of the data suggests the risks may be greater in patients who did not report using ICS at study entry and in African-American patients.
- Overall, the data from SMART suggests a protective effect of concomitant ICS use as reported at study entry. When ICS effect was further analysed by ethnicity, the ICS use at study entry offers a lesser degree of protection for African Americans. However, these post-hoc analysis results are not conclusive.
- As SMART did not assess the ICS dosages actually used by the patients, it is not known whether the increased risks seen with SEREVENT® would also apply to ADVAIR®.
- In the absence of similar data, given the same basic mechanisms of action of long-acting beta$_2$-agonists, it is possible that the findings seen in this study may be consistent with a class effect.

The following is an excerpt of the boxed Serious Warning in the updated SEREVENT® PM:
For the total population studied in SMART (N= 26,355 patients), the risk for the primary endpoint, combined respiratory-related death and life-threatening experience (which included asthma-related outcomes), was 40% higher in the SEREVENT® group compared to placebo (50 out of 13,176 vs 36 out of 13,179; <1% in both cases; relative risk of 1.40 with 95% CI: 0.91, 2.14), and the risk for asthma-related death was increased more than four-fold (13 vs 3; <1% in both cases; relative risk of 4.37 with 95% CI: 1.25, 15.34) during the 28-week randomized treatment period. Increased risks were also observed regarding other respiratory-related outcomes, i.e. respiratory-related death and combined asthma-related death or life-threatening experience. Subgroup analysis suggested that the risk for these serious events may be greater in the African-American population. Furthermore, in patients who did not report using inhaled corticosteroids (ICS) as part of their usual asthma therapy at study entry, there were more asthma related deaths: 9 out of 7,049 (SEREVENT®) vs 0 out of 7,041 (placebo) as compared to 4 out of 6,127 (SEREVENT®) vs 3 out of 6,138 (placebo) for those who did report taking inhaled corticosteroids.

The following Warning has been included in the ADVAIR® PM:
ADVAIR®/ADVAIR® DISKUS® are combination products of salmeterol (a long-acting beta$_2$-agonist) and fluticasone propionate (an ICS). However, since the SMART study did not assess the ICS dosages actually used by the patients, and may be different from those in the ADVAIR® combination products, it is not known whether the increased risks seen with SEREVENT® would also apply to ADVAIR®/ADVAIR® DISKUS®. The ADVAIR®/ADVAIR® DISKUS® dosage form prescribed should reflect the patient's optimal inhaled corticosteroid requirement.

[1]Unlike Canada, in the US, SEREVENT® may be used alone or in combination with inhaled or systemic corticosteroid therapy and all healthcare professionals are warned that SEREVENT® is not a substitute for inhaled or oral corticosteroids. In SMART, not all patients enrolled were taking doses of ICS at study entry.

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Important Advice for Managing Your Patients:
SEREVENT® is not a substitute for inhaled corticosteroids. The ICS should be continued at the same dose, and not stopped or reduced, when treatment with SEREVENT® is initiated or added to the regular therapy. SEREVENT® or ADVAIR® should not be used to treat acute symptoms, and should not be initiated in patients with significantly worsening or acutely deteriorating asthma, which may be life-threatening.

Asthma patients are advised that they must also use an inhaled corticosteroid if they are using SEREVENT®. Patients should not stop or reduce their inhaled corticosteroid dosage without consulting with their physician. Long-acting $beta_2$-agonists are controller medications for the maintenance treatment of asthma and should never be used to treat acute symptoms (i.e. as rescue medication). Patients should be educated to recognize the signs of deteriorating asthma control and the need to seek medical attention promptly in such circumstances.

A public advisory will be issued by Health Canada to remind patients of the appropriate use of long-acting $beta_2$-agonists.

SEREVENT® is indicated in the maintenance treatment of asthma in patients four years of age and older with reversible obstructive airway disease, who are using optimal corticosteroid treatment and experiencing breakthrough symptoms requiring regular use of a short-acting bronchodilator. ADVAIR® is indicated for the maintenance treatment of asthma in patients with reversible obstructive airway disease, where the use of a combination product is considered to be appropriate. A complete copy of the revised PM for both SEREVENT® and ADVAIR® are available on the GSK website at http://www.gsk.ca

The identification, characterization, and management of marketed health product-related adverse reactions are dependent on the active participation of health care professionals in adverse drug reaction reporting programmes. Any occurrences of serious and/or unexpected adverse reactions in patients receiving SEREVENT® or ADVAIR® should be reported to GSK or the Marketed Health Products Directorate at the following addresses:

GlaxoSmithKline Inc. 7333 Mississauga Road N Mississauga, Ontario L5N 6L4 Tel: 1-800-387-7374	Canadian Adverse Drug Reaction Monitoring Program (CADRMP) Marketed Health Products Directorate HEALTH CANADA Address Locator: 0701C OTTAWA, Ontario, K1A 0K9 Tel: 613-957-0337 or Fax: 613-957-0335 **To report an Adverse Reaction, consumers and health professionals may call toll free:** Tel: 1-866-234-2345 Fax: 1-866-678-6789 cadrmp@hc-sc.gc.ca For other inquiries, please refer to contact information. The AR Reporting Form and the AR Guidelines can be found on the TPD web site or in *The Canadian Compendium of Pharmaceuticals and Specialties.* http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/ar-ei_form_e.pdf http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index_e.html

Your professional commitment in this regard has an important role in protecting the well-being of your patients by contributing to early signal detection and informed drug use. Any questions from health care professionals may be directed to our Medical Information department via GSK Customer Service at 1-800-387-7374.

Sincerely,

Dr John A Dillon MB BCh MFPM
VP, Medical Division and Chief Medical Officer
GlaxoSmithKline Inc.